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THE PHYSIOLOGIC CHEMISTRY OF URIC ACID.[1]

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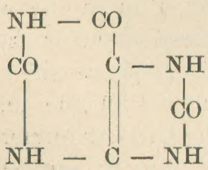
I SHALL not attempt to discuss with any detail the chemistry of uric acid. This would require more space than I have at my disposal. Moreover, this subject has been elaborately treated in various textbooks and I shall devote my time to the less widely known facts concerning the formation of uric acid in the body and the influence of various physiologic and pathologic conditions on the same. I am sure that a discussion along this line will be of more practical interest to medical men than a statement of the more purely chemic facts concerning uric acid.

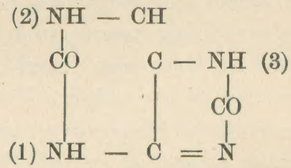
The discovery by Horbaczewski that uric acid is formed when spleen-nucleus is broken up in the presence of oxidizing agents, such as fresh blood or dilute solutions of hydrogen dioxid, has given us the true explanation of the origin of uric acid in the mammalian body and has served as the basis of numerous researches, some of which have already proved of value to the science of medicine. Before this discovery, the chemist had taught us to regard uric acid as a result of imperfect oxidation, the completed product of which is urea, but the physiologist has been unable to satisfactorily demonstrate this supposed relationship between urea and uric acid. The experiments of Horbaczewski show that the amount of uric acid and other xanthin-substances formed in the body is a measure of nuclein-metabolism. In other words it indicates

[1] Read before the Association of American Physicians, May, 1898.

the relative number of nucleated cells that are at the time undergoing disintegration-processes. The researches of Hoppe-Seyler, Miescher, Kossel, and others, on the nucleins, opened up the way for the discovery of Horbaczewski and have since confirmed and amplified the value of his research.

Uric acid belongs chemically and physiologically to a group of substances sometimes known as nuclein-bodies because they have their origin in cell-nuclei. In this group, beside uric acid, we find adenin and hypoxanthin or sarkin (known as the sarkin-bodies), guanin, xanthin, heteroxanthin, paraxanthin, theobromin, theophyllin, caffein, and carnin. All of these, with the exception of uric acid, are basic in character and are generally designated as xanthin-bases. Kossel and Krüger have proposed that these bases, together with uric acid, might be designated as alloxuric bodies, because all of them contain both alloxan and urea residues. The constitution of uric acid and xanthin is shown by the following formula, determined by Fischer:


Uric acid.


Xanthin.

It will be seen that xanthin contains three imido-groups, and by the replacement of a hydrogen-atom of either of these with a methyl-group a monomethyl-xanthin results. Three monomethyl-xanthins are possible, in accordance with the imido-group replaced. Krüger and Solomon have shown that heteroxanthin is a monomethyl-xanthin, with a methyl-group substituted for the hydrogen of the imido-group in position (3). By the substitution of two methyl-groups

three compounds are possible. Theobromin is formed in this way by substitutions in the imido-groups (2) and (3), and theophyllin by substitutions in groups (1) and (2). Paraxanthin is probably the third dimethyl-xanthin, but this has not been positively demonstrated. Caffein is trimethyl-xanthin. Theophyllin and caffein are not known to be constituents of the animal body, but the fact that they are constituents of beverages quite universally employed by man renders their close chemic relationship to other members of this group a matter of physiologic interest.

I have stated that the amount of the alloxuric bodies formed within the organism is a measure of the extent to which nuclear disintegration is going on. It will, therefore, be desirable to inquire into the chemic constituents of cell-nuclei, because we must there find the antecedents of the alloxuric bodies. It is probably true that no two kinds of cells have nuclei of exactly the same composition. Differences in function indicate variations in chemic composition and structure, and, so far as cellular chemistry has advanced, this indication has been confirmed. It will be best to review briefly the facts that have been so far ascertained concerning the chemic composition of cell-nuclei.

The lymphocytes of the thymus-gland have large nuclei that constitute the greater part of the cell, and for this reason, as well as from the fact that they can be obtained in abundance and quite free from other tissue, these corpuscles furnish suitable material for the study of the chemic composition of the cell-nucleus. Lilienfield has made a most valuable contribution to our knowledge of the composition of nuclear substance in his researches on these lymphocytes. He has found that in the dry state these corpuscles yield more than 68% of a body to which he has given the name nucleo-histon, and less than 2% of albumin. These figures

probably fairly represent the relative amounts of nuclear substance and cytoplasm in these cells. It may be remarked that Lilienfield has found nucleohiston not only in the lymphocytes of the thymus and lymphatic glands, but also in the cells of the spleen, the testicles, the unripe spermatozoa of the carp and in the epithelial cells of the small intestine. This nucleohiston is probably identical with the "tissue-fibrinogen" with which Wooldridge, some years ago, secured immunity against experimental anthrax, and which he believed was a compound of lecithin and an albumin.

Nucleohiston may be extracted from finely divided thymus-glands with water, and precipitated from its aqueous solution with acetic acid, avoiding an excess in which the recently precipitated body is soluble. The moist substance is soluble in dilute acids and alkalies and in dilute neutral salt-solution. It is worthy of note that nucleohiston gives the Millon and xanthoproteic reactions, and the biuret-coloration faintly on standing. It contains a little more than 3% of phosphorus. Novy has found that subcutaneous injection of 0.3 gram or more in rabbits causes elevation of temperature of from 1° to 1.5° C., preceded by a short period of subnormal temperature. Nucleohiston, as well as its nucleinic-acid constituent, precipitates diphtheria-toxin, but, as Novy states, this undoubtedly is a mechanical effect; the toxin being carried down with the precipitated proteids. However, nucleohiston does have some destructive action on diphtheria-toxin after the mixture has stood for some time in vitro, although separate injections do not protect animals. (Novy.)

Nucleohiston is easily broken up into histon and nuclein. This can be accomplished by artificial gastric digestion or by the action of 0.8% hydrochloric acid on an aqueous solution, or by boiling the aqueous solution. The nucleins obtained from nucleohiston by

these different methods are very similar, but apparently not identical.

Histon was discovered by Kossel, in 1884, in the nuclei of the red corpuscles of the goose. It has marked basic properties, but in other respects it resembles the peptones. It gives the biuret-reaction. Histon is precipitated from its aqueous solution by saturation with neutral salts; thus a relationship to the globulins is indicated. Its basic character is shown by the fact that it is thrown down from aqueous solution of its hydrochlorid on the addition of ammonia. When injected intravenously histon destroys the coagulability of the blood, but histon-plasma is quite unlike so-called peptone plasma. The views of Lilienfield on the influence of nucleohiston and its components on the process of coagulation will be stated later. Novy has shown that histon is much more poisonous than Lilienfield believed. Two hundred milligrams often killed guinea-pigs weighing 300 grams or less. Repeated injections not only failed to establish tolerance, but apparently increased susceptibility. Necrotic areas often formed about the point of inoculation in animals that recovered. The effect on the temperature is similar to that of nucleohiston. From the results obtained by Wooldridge and some subsequent investigators, it has been suggested that histon might have antitoxic properties. The careful researches of Novy on this point fail to confirm this belief. He finds that histon does not protect against separate subcutaneous injections of the toxins of diphtheria and tetanus, or against inoculations of the bacilli of anthrax and hog-cholera; that, in a mixture of histon and diphtheria-toxin, the latter is destroyed in a few minutes, but that this is due in part, if not wholly, to the acidity of the histon-solution.

Leukonuclein, the body conjugated with histon in

nucleohiston, is easily decomposed into an albuminous substance and nucleinic acid. With the former we are not concerned, but nucleinic acid is, for the purpose of the present inquiry, the most important constituent of the nucleus. Nucleinic acid is characterized (1) by its large phosphorus-content, nearly 10%; (2) the fact that on being broken up it yields xanthin-bases; and (3) its marked germicidal properties. All nucleinic acids, so far as studied, those from yeast-cells, spleen, marrow, spermatozoa, nervous tissue, the thymus, etc., are bactericides. This property of the nucleins, discovered by myself in 1893, has been confirmed by Kossel and others. To furnish the germicidal nucleinic acid is apparently one of the most important functions of the leukocyte, and in setting free this substance the corpuscle itself most probably is destroyed.

Although it has no direct bearing on the physiology of uric acid, it may be of interest to insert at this place Lilienfield's views concerning the influence that nucleohiston and its components have upon the coagulation of the blood. He says:

"The leukocytes contain in their nuclei a markedly acid substance, nucleohiston, which, when added to spontaneously coagulable fluids, or to cold, filtered horse-plasma, or to proplastic and fibrinogen fluids treated with fibrin-ferment, retard their coagulation greatly. Caustic lime and caustic baryta split up nucleohiston into leukonuclein and histon. Nucleohiston dissolved in lime or baryta-water causes coagulation in proplastic and fibrinogen fluids. From the above the following conclusions may be drawn: (1) Histon is the coagulation-retarding constituent of nucleohiston; (2) leukonuclein is the coagulation-hastening constituent. Naturally after having the histon split off, nucleohiston loses its retarding action on coagulation. Leukonuclein and nucleinic acid are not in and of themselves capable of producing fibrin from fibrinogen. They split off from fibrinogen thrombosin, the immediate antecedent of fibrin, and then, on the addition of a soluble lime-salt, thrombosin is converted into fibrin. By employing a solution of nuclein in lime-water both steps in the process are accomplished. The nuclein splits off the thrombosin, which in the lime-solution passes into fibrin. . . The intensity of this effect is in direct pro-

portion to the amount of nucleinic acid in the nucleoproteid molecule, and is greatest when nucleinic acid itself is used. . . Fibrin is a lime-compound of thrombosin."

Lilienfield found that neutral solutions of nucleohiston injected into the jugular vein of living animals caused the formation of thrombi, while the blood allowed to flow from the carotid remained fluid. Injection of neutral solutions of histon-hydrochlorid to the extent of 0.3 gr. to each kilo of body-weight renders the blood subsequently drawn noncoagulable. Injection of neutral leukonuclein-solution causes the formation of thrombi, and the blood subsequently drawn coagulates instantaneously.

It must not be inferred that all nucleinic acids cause coagulation of the blood. I have injected large quantities of yeast nucleinic acid intravenously in rabbits and as much as one gram of this acid in man without causing any such effect. Moreover, the statements of Lilienfield, as quoted, have been very properly criticised by Cramer, who believes that Lilienfield's so-called thrombosin is nothing more than fibrinogen.

It is possible that the slowness with which blood sometimes was seen to coagulate in the old days of venesection, giving time for the partial subsidence of the red corpuscles and the formation of the "buffy coat" of leukocytes, was due to the presence of an unusual quantity of histon in solution, and that our professional ancestors were not far out of the way when they attributed this phenomenon to an "inflammatory" condition of the blood.

Nucleinic acid, on being decomposed, yields the nuclein-bases and thymic acid. The kind and amount of nuclein-bases yielded by different nucleinic acids are by no means constant. Yeast nucleinic acid, on being heated with a dilute mineral acid, yields relatively large quantities of adenin, hypoxanthin, guanin,

and xanthin. In his earlier work on thymus nucleinic acid, Kossel was able to detect among its decomposition-products only one of the nuclein-bases, adenin, and he proposed that this nucleinic acid should be called adenylic acid. More recently, however, he has found, in addition to adenin, not only guanin, but also a new base, cytosin. It will be best, for the present at least, to designate the different nucleinic acids by the source from which they are obtained, and we shall continue to speak of yeast nucleinic acid, thymus nucleinic acid, etc. Of thymic acid it is necessary to say only that it contains all the phosphorus present in the original nucleohiston-molecule, and that it can be decomposed into a base, thymin, and levulinic and phosphoric acids. The following represents the steps in the breaking up of the molecule of nucleohiston :

$$\text{Nucleohiston}\left\{\begin{array}{l}\text{Histon,}\\ \text{Nuclein,}\left\{\begin{array}{l}\text{Albumin,}\\ \text{Nucleinic acid,}\left\{\begin{array}{l}\text{Nuclein-bases,}\\ \text{Thymic acid,}\left\{\begin{array}{l}\text{Thymin,}\\ \text{Levulinic acid,}\\ \text{Phosphoric acid.}\end{array}\right.\end{array}\right.\end{array}\right.\end{array}\right.$$

I have gone somewhat into detail concerning the composition of the nucleus of the leukocyte, because when we come to study the phenomenon of chromatolysis, in which process uric acid is formed, we must know something of the antecedents and the by-products before we can estimate the cost or appreciate the real value of the special product. Indeed, I must say a few more words concerning the chemic composition of nuclear substance. In many cells the basic histon is not present, and in its place there is formed a basic proteid of much simpler molecular structure. These proteid bases are known under the general name of protamins. Miescher, who may be regarded as the discoverer of nuclein, obtained in 1874 a basic substance

from the spermatozoa of salmon, to which he gave the name protamin. This base is combined in these cells with nuclein. In 1894 Kossel took up the study of protamin, and he has since shown that in the spermatozoa of many animals there are proteid bases combined with nuclein. In no two animals are the basic substances identical, and Kossel proposes that the name protamin be used generically, and he calls the base obtained from the spermatozoa of the salmon, salmin, and that from the sturgeon, sturin. Kossel is of the opinion that a protamin-group will be found in all proteids, and that it is from this group in the proteid molecule that leucin and basic substances are derived. He is also inclined to the opinion that the histon of nucleohiston consists of a protamin combined with an albumose. In fact he has prepared such a compound, which, he states, gives all the reactions of histon. However, before it can be definitely shown that the protamin-group is contained in histon it must be shown that protamin-derivatives can be obtained from histon. On being heated with sulphuric acid and water a protamin can be split up into histidin and arginin. The last-mentioned base was discovered by Schulze in the conglutin of lupin-sprouts, and later was obtained by Hedin in the decomposition of horny substance with hydrochloric acid and stannous chlorid. Schulze and Sikiernik have shown that arginin on being heated with baryta yields urea. The protamin-molecule contains the basic group, but does not contain the tyrosin or amido-acid group. This encourages us to hope that the structure of the proteid molecule will some time be known.

Recently H. Kossel has demonstrated the very interesting and important fact that the protamin, sturin, has marked bactericidal properties. This shows that the nucleated cell contains in addition to its nucleinic acid a germicidal basic substance, and is additional evidence

that certain animal cells are well protected against bacterial invasion.

Mathews, working under Kossel, has recently studied the spermatozoa of the boar, bull, herring, and the sea-urchin, arbacia. He finds that the sexual cells of the herring consist principally of nucleinic acid combined with a protamin to which he gives the special name clupein; that the basic substance in the spermatozoa of the sea-urchin is more nearly related to histon than to protamin; and that those of the bull and boar contain neither protamin nor histon.

We are now ready to proceed to the study of the origin of the alloxuric bodies in the body. It will be evident from what has already been said concerning the chemistry of nuclear substances that the alloxuric bodies can originate only when there is nuclear disintegration, and then not until the nucleinic acid is broken up. The dissociation of the basic substance and the nuclein is not enough to lead to the formation of the alloxuric bodies. Indeed, nucleinic acid may be set free and manifest its germicidal action without the production of uric acid and its immediate antecedents. The destruction of the nuclear substance must be quite complete before these bodies are formed. The solution and disintegration of nuclei are designated as the process of chromatolysis. Some of the conditions under which the alloxuric substances may be formed in the body may now be stated.

(1) Every nucleus comes from a parent-nucleus. Every cell must at some period of its existence be nucleated. No cell can be built up or organized except through the agency, direct or indirect, of a nucleus. Every cell that is capable of reproduction must contain a nucleus. I do not mean to say that a certain amount of cytoplasm is not also necessary to reproduction. There may be some difference of opinion on this point,

or the nuclei of some cells may require cytoplasm, while the nuclei of other cells may not, but there can be no doubt that the existence of a nucleus is essential to the process of reproduction. However, this is not the sole function of the nucleus. As has already been stated, the nucleus is essential to the organization of the cell; cells that are never to reproduce themselves are organized through the agency of nuclei. Biologically, the nucleus is that part of the cell which is essential for growth and reproduction. Quantitatively, it may constitute the greater part of the cell, or it may be relatively a very minute fraction of it. Developmentally, it is that part of the cell that determines both form and function. From the standpoint of heredity the nucleus is that part of the cell through which generic and specific form and function are transmitted. It is that part of the cell that makes life, potentially at least, continuous. Nuclein is the material of which nuclei are composed. Many of the cells formed in the animal body are destined, after having reached a certain period of growth, solely to serve other cells. These may, and some of them certainly do, lose their nuclei after having reached the stage of development necessary for them to reach before they can perform the function for which they are brought into existence. Chromatolysis and cell-disintegration are not in these cells simultaneous processes. The erythrocytes of mammals are cells of this kind. Erythroblasts may be studied in the spleen and bone-marrow of both young and adult animals. (The formation of erythroblasts in the spleen of the adult animal in a normal condition is slight, and some deny that it occurs.) I shall not enter into a description of the well-known changes observed in the formation of these cells. I wish only to call attention to the fact that the nucleus, after having perfected the red blood-corpuscle, so that it may serve as

a carrier of oxygen, disappears, and, so far as we know, is not further utilized. The suggestion that the nuclear substance of the erythroblasts, after having performed its function in the organization of the cell, may be utilized in the building up of some proteid of the plasma, does not affect the general statement here made, even if it be true. It matters not for the present purpose whether the chromatolysis observed in these bodies be accomplished by a gradual solution of the nuclein or a more active expulsion of the nucleus, the result is the same in either case. Nuclein is broken up, alloxuric bodies are formed, and uric acid, the most highly oxidyzed of these substances, is the chief representative, in the urine, of the nuclear metabolism resulting, as here indicated, in the body. As the formation of red blood-corpuscles is a continuous process, this source of the alloxuric bodies is a never-failing one. The modifications to which it is subject in disease need not be discussed here. During fetal and early extrauterine life, the number of cells undergoing this kind of chromatolysis must be relatively much greater than subsequently. It must not be inferred that chromatolysis, without simultaneous cell-disintegration, is confined to the red corpuscles. I have referred to these as a suitable illustration of a process that goes on to a greater or less extent in other tissues.

(2) The leukocytes are a constant but quantitatively variable source of uric acid and other alloxuric bodies. The biology of the leukocyte is one of the most interesting problems in medicine. Within a few years past it has been demonstrated that an increase in the number of leukocytes in the blood is followed by increased elimination of alloxuric bodies. However, there are exceptions to this rule. It is too early yet to attempt a scientific classification of the different forms of hyperleukocytosis and hypoleukocytosis. However,

this need not deter us from gathering together the somewhat meager and incomplete facts on the subject and endeavoring to read the lessons they teach.

There may be hyperleukocytosis without consequent increase in the amount of alloxuric bodies eliminated. The researches of Kühnau have demonstrated this. It has long been known that the intravenous injection of inert substances, such as cinnabar or carbon in finely divided form, will cause a great increase in the number of leukocytes in the blood. After a short time no free particles of the dust can be found in the blood, but the leukocytes are laden with the particles. Hoffmann and Langerhans observed these pigment-bearing corpuscles 20 days, and Ponfick 70 days, after the injection of the dust. They are found most abundantly in the small capillaries, where the leukocytes undoubtedly have the best opportunity to absorb them, on account of the slow movement of the foreign particles. Then the leukocytes bear the foreign particles out of the blood-vessel and, apparently at least, permanently deposit themselves with their burden in some extravascular cell. I say apparently, because we cannot positively assert that the corpuscles remain permanently with the particle. However this may be, the studies of Kühnau have shown that there is no increased elimination of alloxuric bodies following the most marked hyperleukocytosis induced in this manner. These experiments are of further interest inasmuch as they indicate that the life of the leukocyte may be much longer than is usually supposed to be possible.

In the second place, there may be hyperleukocytosis with increased elimination of the other alloxuric bodies, but with no increase and sometimes with a marked decrease in the amount of uric acid formed and eliminated. This seems to be true in the graver anemias. However, more extended investigation along this line is

desirable. Kühnau suggests that this may be ascribed to deficient oxidation due to the great decrease in the red corpuscles, as Hobaczewski has shown that nuclein must be broken up in the presence of an oxidizing agent in order to yield uric acid. It should be stated that it is not supposed that the xanthin-bases are formed and then oxidized into uric acid. When nuclein is oxidized and then broken up it yields uric acid and the xanthin-bases. When broken up without previous oxidation, it yields the xanthin-bases, but no uric acid. Kolisch and Stejskal report a case of grave anemia, terminating in death within a few days, in which the uric acid was much below, and the xanthin-bases greatly above, the normal. The studies of Neusser and of Westphal, in which the former reported an excess and the latter a deficiency of uric acid in pernicious anemia, do not throw any additional light on this subject, inasmuch as they failed to estimate the other alloxuric bodies. The experimental studies in which the red corpuscles have been destroyed by the use of some dissolving agent show somewhat diverse results. However, it is, so far as I know, quite generally true that marked destruction of the red corpuscles is accompanied or followed by hyperleukocytosis, the increase in the leukocytes being absolute as well as relative. I believe this to be true of malaria, although the evidence on this point has been somewhat conflicting. The difference in the observations is apparently due to the time with reference to the paroxysm when the leukocytes have been counted. Kühnau probably states the facts correctly when he says that during the paroxysm blood-pigment is set free. The large polymorphonuclear leukocytes in the spleen and marrow absorb the red-corpuscle detritus, infected red-corpuscles and entire plasmodia. During this stage the leukocytes will be found in diminished number in the blood.

After the paroxysm the melaniferous leukocytes appear in the blood. This is the stage of hyperleukocytosis. It is of short duration and is followed by leukolysis and a consequent increase in elimination of both uric acid and the other alloxuric bodies. The same investigator found a similar decrease in the red-corpuscles, with subsequent hyperleukocytosis and augmented elimination of alloxuric bodies after subcutaneous injections of pyrogallol. A priori, it might be inferred that the hemoglobin from the broken-down red corpuscles is the leukotactic substance, but Kühnau found that intraperitoneal injections of hemoglobin have but slight leukotactic or leukogogic effect.

In the majority of instances of hyperleukocytosis there is subsequent leukolysis and a consequent augmentation in the amount of alloxuric bodies, including uric acid. This is true of digestion-leukocytosis and of that which follows the injection of nuclein. It is also true of the leukocytoses that accompany various inflammatory diseases.

It would be of great interest to know the successive products that result in disintegration of the leukocytes. Much more extended and exact research is necessary before we can speak very definitely on this point. However, the idea that the value of a hyperleukocytosis in combating an infectious disease is to be measured by the number of leukocytes, without reference to the agent used to increase their number, is certainly wrong. That hyperleukocytosis induced by nuclein and allied bodies does augment the germicidal properties of the blood and increase the resistance of the animal body against certain pathogenic microorganisms has been demonstrated by the researches of Wooldridge, myself, Grammatschikoff, Pawlòwski, Loewy and Richter, Hahn, Jacob and others. These have uniformly found that a nuclein-hyperleukocytosis does slightly increase

the resistance of the body against bacterial infection. All, furthermore, conclude that the extent to which the resistance can be increased by this means is, with present means, limited. That every hyperleukocytosis does not increase the resistance to infection has been shown by direct experiment. It is well known, for instance, that the injection of pilocarpin causes an extraordinary hyperleukocytosis, and yet an amount of a culture of the pneumonococcus from which the control might escape and the nuclein-animal would surely not be affected, kills the pilocarpin-animal, notwithstanding the great increase in leukocytes. Whether this is due to the depressing action of pilocarpin on the heart, as supposed by Loewy and Richter, or to some other cause, cannot be at present stated. It is certainly true that in some forms of leukolysis, nucleinic acid is set free, and to this must be ascribed the increased germicidal action of the serum obtained from hyperleukocytotic blood. It has been found to be necessary to modify the phagocytic theory of Metschnikoff. It is now generally agreed that the leukocytes combat the bacteria by virtue of some chemic constituent of the former.

The question now is whether we are to believe with Buchner that his so-called alexins are secretions of the leukocytes, or that the leukocyte disintegrates, and that one or more of the substances resulting from this disintegration act as germicidal agents. Havet seems to have been the first to show that in hypoleukocytosis the germicidal action of the blood is reduced, while on the other hand, in hyperleukocytosis the bactericidal action is augmented. Hahn has confirmed the second half of this statement.

The following reasons may be given for the belief that the increase in the germicidal properties of the blood following hyperleukocytosis is due to leukolysis and is not a result of an increased secretion of a germicidal substance by the leukocytes:

(*a*) By artificially breaking up the leukocytes outside the body a germicidal substance, nucleinic acid, is obtained; (*b*) increased elimination of the alloxuric bodies follows hyperleukocytosis in all instances with the exceptions already stated; (*c*) the microscopic studies of Botkin and Löwit show that hyperleukocytosis is followed by an increased quantity of leukocytic debris in the blood; (*d*) the experiments of Loewy and Richter show that hyperleukocytosis is followed by the appearance in the blood of albumoses that are not found under normal conditions, or are found only in minute traces. These albumoses are believed to come from the disintegration of the leukocytes. However, I must state that I do not consider the method employed by these investigators wholly free from chances of error.

Experiments made to determine whether or not change in leukocytotic content alters the glycolitic property of the blood have been contradictory, and consequently do not furnish evidence for either side of this question.

Whether the hypoleukocytosis that immediately follows the injection of nuclein, albumose, bacteria, toxins, etc., is due to leukolysis or to leukopenia has not been positively determined.

(3) A third source of uric acid and allied bodies is the food. It has long been known that increased consumption of animal food increases the amount of uric acid formed in the body. This increase is probably due to two causes: (1) Meat contains nucleo-proteids and alloxuric bodies in small amount. (2) Digestion-leukocytosis is greatest after meals rich in animal food and is likewise increased by alcoholic beverages. The fact that nuclein-containing foods increase the amount of alloxuric bodies formed and eliminated has been demonstrated by several investigators, among whom

may be mentioned Umber, Mayer, and Hess and Schmoll. It is needless to dilate upon these statements.

(4) The physiologic disintegration of various nucleated cells in the body must contribute slightly to the formation of alloxuric bodies. This is especially true of epithelial and glandular cells. According to the studies of Weintraub, 100 grams of meconium contain from 0.3 to 1.0 gram of uric acid, and the daily stool of an adult from 0.1 to 0.5 gram of alloxuric bases.

(5) Some poisons, such as lead and alcohol, stimulate certain cells to abnormal proliferation. Karyokinesis assumes pathologic significance and many of the rapidly forming cells break down and their nuclei suffer dissociation-changes.

(6) Certain pathologic growths are accompanied by marked cell-proliferation and, as many of these cells, including their nuclei, disintegrate, this may be a source of uric acid and allied bodies in cases of carcinoma, etc. However, the scope of the work assigned me does not require me to go into a discussion of a pathologic condition, and I gladly leave their consideration to those who can speak more authoritatively.

H.